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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/964,042	WEICHSELBAUM ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Action is in response to the Amendment filed 7/19/02, as Paper No. 6. The response has been entered and claim 1 has been amended. Claims 1-9 are pending in the application. Unless otherwise indicated, arguments directed to rejections that are rendered moot in view of Applicants amendments will not be further addressed.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office Action of 1/15/02 and for the reasons set forth below, because the specification, while being enabling for the reduction of tumor mass (i.e. treatment) by direct injection into a tumor in an immunologically compromised (athymic) mouse, using a specific attenuated HSV R7020 mutant (comprising the specific modification described in the specification), does not reasonably provide enablement for treatment in any and all "individuals" via any route of administration other than direct injection and wherein the virus comprises any modification in an inverted repeat region.

The rejection is maintained primarily because the claims are broadly written and encompass the reduction of tumor size in any individual, including humans, wherein the therapeutic virus can be delivered by any administration, including systemic administration. Applicants have argued that the method would work, as evidenced by the Examples present in

the specification. It is respectfully pointed out, however, that the Examples only indicate the reduction of tumor cells in nude mice by direct injection of the therapeutic virus into the tumors. There is no evidence presented that systemic administration (or any administration other than direct injection) would result in the reduction of tumor mass in any individual other than a nude mouse. Furthermore, the teachings of Advani (see below) indicate that the available data in experimental animals do not predict a high cure rate for humans. Therefore, because the claims are not limited to the direct injection of the therapeutic virus into the tumors, the rejection is maintained. Limiting the scope of the claims to the direct injection of the virus into the tumors would obviate this rejection. Each of the applicant's arguments is addressed below.

The following factors have been determined by the courts to be critical in determining whether a claimed invention is enabled (See In re Wands 8 USPQ 2d 1400, Fed. Cir. 1988).

The nature of the invention: The instant claims are drawn to a method for reducing tumor mass in an "individual" comprising administering an amount of recombinant Herpes simplex virus (HSV) wherein said HSV genome comprises a modification of an inverted repeat region such that one $\gamma_1$34.5 gene remains intact and where in said amount of HSV is being effective to reduce tumor mass. Thus, the nature of the invention is a therapeutic use of attenuated HSV virus for treating tumors and generally falls in the realm of gene therapy, and specifically encompasses oncolytic virotherapy.

The state of the prior art and the predictability or unpredictability of the art: At the time of filing, the relevant art considered gene therapy as a whole to be extremely unpredictable. Efficacious, predictable modes of delivery that

would provide efficient delivery and expression of genes encoding the protein in the target cells had not been developed. Regarding the specific delivery of therapeutic viruses to targeted cells, **Verma et al.,** (1997) states that delivery is the "Achilles heel", and indicates, "[t]he use of viruses is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses" (pg. 293, col. 3, parag. 1). **Chamber** et al., (1995) previously attributed the greater survival benefit for glioma-bearing mice treated with a $\gamma_1$34.5 mutant in which the 34.5 gene is interrupted by a stop codon (R4009) rather than by deletion (R3616) due to the low level of stop codon suppression in R4009 allowing for enough viral replication so as to effectively destroy tumor cells, yet not multiply to a level where it can cause encephalitis and taught that the "key to the development of effective oncolytic viruses may well depend on precise control of the expression of the $\gamma_1$34.5 gene" and that "this observation may be exploited to construct still more effective viruses" (page 1415, left column). **Advani** (1998) teaches that "While attenuated herpesviruses alone have not been tested in humans, the available data in experimental animals do not predict a high cure rate (page 162, left column) and that "infection alone produced few cures and the majority of infected tumors either grew more slowly or outpaced cell destruction" (page 162, top right column). **Crystal** (1995) has previously recited that "human are not simply large mice. There have been several surprise examples, in which predictions from gene transfer studies in experimental animals have not been borne out in human safety and efficacy trials" (page 409, bottom, left column). Without an art recognized nexus between the results obtained in animal models and the

results which the skilled artisan would reasonably expect to see in humans, the results of applicants animal model data are difficult or impossible to interpret.

Specifically regarding the use of nude mice as human cancer models, Trisha **Gura** teaches in her article titled "Systems for identifying new drugs are often faulty" (Science, 1997; 278:1041-1042),

> "Pharmaceutical companies often test drug candidates in animals carrying transplanted human tumors, a model called a xenograft. But not only have very few of the drugs that showed anticancer activity in xenografts made it into the clinic, a recent study conducted at the National Cancer Institute (NCI) also suggests that the xenograft models miss effective drugs. The animals apparently do not handle the drugs exactly the way the human body does." (See p. 1041, first column)

Gura also teaches, "xenografts tumors don't behave like naturally occurring tumors in humans—they don't spread to other tissues for example. Thus, drugs tested in the xenografts appeared effective, but worked poorly in humans." (See p. 1041, column 2).

Furthermore, **Kerbel** teaches (see "What is the optimal rodent model for anti-tumor drug therapy?" Cancer and Metastasis Reviews Vol. 17:301-304; 1999), "A recurring problem with the use of present models of transplantable tumors is that they frequently respond to anti-cancer drugs or other therapies which then show no activity in humans." (see p. 301, first column). Kerbel indicates a number of specific problems with the mouse model, including (i) concentrations of drugs are used at the maximum tolerated doses for mice, not humans—it turns out that the maximum tolerated dose for mice is often significantly greater than it is for man (see p.301, first column); (ii) most transplanted tumors are very fast growing—drugs are often designed to target rapidly dividing cells; however, natural human tumors often grow much slower. Therefore, the transplanted tumors can show an "exaggerated" response to a drug (see p. 301, second column); and (iii) the response to therapy of a single 'primary' growing transplanted

tumor mass is usually what is evaluated rather than that of distant metastases. Regarding (iii), Kerbel teaches, "Clearly this is not representative of most clinical treatment situations in which distant metastases are the target of systemic therapy, and not the primary tumor, which is generally dealt with using surgery." (See p. 302, column 1).

The above references acknowledge the usefulness of gene therapy for the treatment of cancer and other diseases in the future, however, they also illustrate that there are numerous obstacles that the specification would need to overcome.

The breadth of the claims and the amount of direction or guidance presented in the specification and the presence or absence of working examples:

As such, the disclosed claims are very broad and read on killing any type of tumor by delivering the attenuated HSV by any route to an individual. Clearly, systemic administration of an attenuated oncolytic herpesvirus by intramuscular injection will have little or no efficacy against a glioblastoma, wherein the blood brain barrier restricts entry into the brain of 120 nm HSV particles (**Muldoon** et al., 1995). Also, the specification does not provide sufficient guidance on which mutants to use beyond HSV $\gamma_1$34.5 mutants or which HSV $\gamma_1$34.5 mutants exhibit the requisite level of $\gamma_1$34.5 expression in accordance with the teachings and considerations disclosed by **Chambers** et al., (1995). That is the statement concerning lack of reference between the in vivo nude mouse model data presented by applicants and results which skilled artisan would expect in humans. Without guidance from the specification or the prior art, empirical experimentation would be required to determine an effective amount to treat glioblastoma, prostate adenocarcinoma and hepatoma in the individual.

The quantity of experimentation: To attempt to practice the claimed invention in humans, one of skill in the art would turn to the specification for guidance in practicing the invention. As set forth above, however, the specification lacks sufficient guidance to surmount the technical difficulties recognized in the art. Another source of guidance for one skilled in the art, the prior art, again for reasons set forth above, also lacks solutions to overcome the considerable list of obstacles recognized in the field. In the absence of working examples from the specification and the prior art, one of skilled in the art would resort to trial and error experimentation to navigate the obstacles to practicing the claimed invention. Again, as established above, solutions to these technical problems have been elusive despite an enormous amount of experimentation due to a number of factors, including the unpredictable nature of the art. Such unpredictability would warrant even more experimentation, with no true expectation of a measure of success. The amount of experimentation required to practice the claimed invention embodiments would necessitate undue experimentation on the part of one skilled in the art.

In conclusion, given the nature of the invention, the state of the art, the lack of predictability found in the art, the breadth of the claims, the amount of guidance set forth in the specification, and the working example set forth it is concluded that the amount of experimentation necessary to practice the full scope of the claims is very high and is in fact undue.

Response to Arguments

Applicant's arguments filed 7/19/02 have been fully considered and are persuasive only to the extent that the method is enabled for reducing tumor size of epidermal carcinoma, prostate

adenocarcinoma and hepatoma adenocarcinoma in nude mice (as mentioned above) when the virus is administered by direct injection. The claims are very broad and encompass the reduction of any kind of tumor in any individual (e.g. humans) by any type of administration, including systemic administration wherein the virus comprises any type of modification in any inverted repeat region of the HSV. Therefore, the arguments are not fully persuasive because the claims encompass embodiments which are not enabled. The non-enabled embodiments are addressed below in response to Applicants arguments.

First, Applicants contend that the Invention has been categorized as "gene therapy" (p. 3), which requires a very broad interpretation of the Invention. Applicants correctly point out that the present invention does not rely on the expression of a gene of interest for therapeutic purposes, the classical definition of gene therapy. It is acknowledged that the present invention is not classical "gene therapy" (given the aforementioned definition), but rather oncolytic virotherapy, which involves the administration of a therapeutic virus. However, many of the problems recognized in classical gene therapy are inherent to oncolytic virotherapy. For instance, specific delivery of a therapeutic virus to the target cells, and the effect of immune response on the therapeutic virus are problematic issues that are common to both gene therapy and virotherapy. It is respectfully pointed out that classical "gene therapy" encompasses the administration of a virus which specifically delivers a therapeutic gene of interest to target cells. Therefore, the teachings of Verma regarding the recognized problems associated with the administration of a therapeutic virus to a cancer patient are pertinent to both classical gene therapy and to the present invention. As mentioned in the previous Office Action, Verma teaches that the immune response of humans fight off viruses, and attempts to administer

therapeutic viruses have been confronted by these host responses (see Verma p. 293, col. 3). It is acknowledged that the teachings of Verma regarding the expression of therapeutic genes are, however, irrelevant to the present invention.

Second, in response to the teaching of Crystal that experiments in animal models have not been borne out in human safety and efficacy trials, Applicants contend that the nude mouse is recognized as a cancer model and is routinely utilized by those of ordinary skill in the art as evidenced by the submitted exhibits. It is acknowledged that the nude mouse is used extensively in cancer therapy experiments. However, there are problematic issues recognized in the art regarding not only the transfer of results from animals to humans in general (as taught by Crystal), but specifically regarding the use of nude mice as human cancer models. For instance, Trisha Gura teaches in her article titled "Systems for identifying new drugs are often faulty" (Science, 1997; 278:1041-1042) teaches,

> "Pharmaceutical companies often test drug candidates in animals carrying transplanted human tumors, a model called a xenograft. But not only have very few of the drugs that showed anticancer activity in xenografts made it into the clinic, a recent study conducted at the National Cancer Institute (NCI) also suggests that the xenograft models miss effective drugs. The animals apparently do not handle the drugs exactly the way the human body does." (See p. 1041, first column)

Gura also teaches, "xenografts tumors don't behave like naturally occurring tumors in humans—they don't spread to other tissues for example. Thus, drugs tested in the xenografts appeared effective, but worked poorly in humans." (See p. 1041, column 2).

Also, Kerbel teaches (see "What is the optimal rodent model for anti-tumor drug therapy?" Cancer and Metastasis Reviews Vol. 17:301-304; 1999), "A recurring problem with the use of present models of transplantable tumors is that they frequently respond to anti-cancer drugs or other therapies which then show no activity in humans." (see p. 301, first column).

Kerbel indicates a number of specific problems with the mouse model, including (i) concentrations of drugs are used at the maximum tolerated doses for mice, not humans—it turns out that the maximum tolerated dose for mice is often significantly greater than it is for man (see p.301, first column); (ii) most transplanted tumors are very fast growing—drugs are often designed to target rapidly dividing cells; however, natural human tumors often grow much slower. Therefore, the transplanted tumors can show an "exaggerated" response to a drug (see p. 301, second column); and (iii) the response to therapy of a single 'primary' growing transplanted tumor mass is usually what is evaluated rather than that of distant metastases. Regarding (iii), Kerbel teaches, "Clearly this is not representative of most clinical treatment situations in which distant metastases are the target of systemic therapy, and not the primary tumor, which is generally dealt with using surgery." (See p. 302, column 1).

Specifically regarding the administration of therapeutic herpes virus to the immunologically compromised mouse model, Advani (Gene Therapy, 5(2):160-165, 1998) teaches, "[w]hile attenuated herpes viruses alone have not been tested in humans, the available data in experimental animals do not predict a high cure rate" (p. 162, left column).

Therefore, although the nude mouse is utilized to test the efficacy of potential therapeutic drugs, there are a number of art recognized problems that prevent the results obtained in mice from being an accurate predictor of efficacy in humans. Neither the specification nor the cited exhibits present persuasive evidence that overcomes the art recognized problems.

Third, Applicants contend that Example 2 in the specification demonstrates that the Invention does work. It is pointed out that Example 2 indicates that treatment by direct tumoral injection was effective at reducing the volume of specific types of tumors transplanted into nude

mice. Therefore, it is acknowledged that the Invention is enabled for treatment of specific types of tumors in nude mice by direct injection of the specific virus. The claims, however, are broadly written and encompass the treatment of humans by any type of administration of the virus (including systemic administration). Therefore, the claims as written are not fully enabled.

Fourth, with respect to the effect of the immune response against a viral agent, Applicants appear to contend that any drug can be formulated with respect to clearing from circulation via the reticulendothelial system, that the circulatory half life of the drug is usually proportional to the amount of drug administered and, therefore, the teaching of Verma is irrelevant—assumably because the dose can be adjusted to accommodate the host's immune response. The Examiner respectfully disagrees with the Applicants view of Verma's relevancy. The examples in the instant specification involve the administration of the therapeutic virus to a mouse which does not have an immune response. Verma teaches that attempts to administer therapeutic virus have been confronted by the hosts' immune response. Without evidence that the therapeutic virus can be effectively administered to an individual with an intact immune system, there is no indication the treatment can overcome the art recognized problem of the immune response. Looking to the specification for guidance, there is insufficient guidance to determine whether the claimed virus (R7020 attenuated virus), is sufficiently enabled for reducing tumor mass in humans. The animal results do not overcome the unpredictability recognized in the art, since the nude (immunodeficient) mouse model presented does not allow one to evaluate viral replication and tumor mass reduction in the face of the counteracting forces of the immune system, which are known to attack viruses in accordance with the teachings of Verma. Data indicating that the therapeutic virus could be effectively administered as claimed to an individual with an intact

immune response such that the administration resulted in the reduction of tumor mass would be persuasive with respect to this issue.

Sixth, Applicants state the examiner's reliance on the disclosure of Chambers is unclear. In response, it is respectfully pointed out that the claims are very broad and encompass the reduction of any tumor mass in any individual. Therefore, the claims encompass the reduction of a brain tumor mass in a human brain. As mentioned in the previous Office Action, Chambers teaches that control of the replication of the virus is critical because an inadequate amount of replication would result in ineffective treatment, while too much replication could cause encephalitis. Therefore, the Chambers is relevant because it teaches that too much replication of the therapeutic virus in brain tumors could result in negative side effects, such as encephalitis. The instant application does not offer any examples of treatment of a brain tumor with the therapeutic virus. Therefore, it is possible that treatment of brain tumors with the therapeutic virus could cause encephalitis. Furthermore, it would not be a matter of optimizing the parameters in the mouse model for human administration. The instant model system is a mouse model which does not have a functional immune response. Therefore, it would be more than a matter of routine optimization to adapt the method of the animal model to a human with a functioning immune system. Also, Chambers indicates that it is the amount of viral replication in cells in vivo which is critical.

Finally, Applicants contend that the specification demonstrates an operative aspect of the invention against which all alternative aspects can be compared, and that "Optimizing various parameters can therefore be effected using the exemplified method as a positive control. Such an optimization is certainly routine in the art and not undue." (See p. 5). It is acknowledged that the

specification does demonstrate that tumor cell mass can be reduced in nude mice when the therapeutic virus is delivered to the tumor by direct injection. However, the claims encompass reducing tumor mass in humans by administering the therapeutic virus in any fashion, including system administration. This would not be a matter of routine optimization for the reasons discussed above. Furthermore, As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

The lack of human testing, combined with the limited efficacy observed in animal studies conducted using immunologically compromised mice underscores the lack of predictability associated with treatment of normal, non-immunologically compromised "individuals" that are more often than not immunologically primed against herpes simplex virus on account of prior exposure to herpes infections early in life.

Therefore, it would require undue experimentation for one skilled in the art to use the claimed invention commensurate in scope with the claimed subject matter. This is particularly true given the state of the art, the nature of the invention, the unpredictability of the art, the scarcity of guidance and working examples in the specification, and the amount of experimentation necessary.

New Rejections

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims re drawn to a method for reducing the tumor mass by administering an modified HSV wherein the HSV comprises "a modification of an inverted repeat region of said HSV genome such that one γ1.34.5 gene remains intact and said amount of HSV being effective to reduce tumor mass."

Therefore, the instant claims encompass modifications which are different from those disclosed in the specification and include variants for which no written description is provided. This genus is indeterminant in size, however, considering every possible modification encompassed by the claims (such as every possible addition, deletion, inversion, substitution in an inverted region that results in an intactγ1.34.5 gene) the genus is likely to be consist of thousands or perhaps millions of different species. This large genus is represented in the specification by only one modification, an insertion of the HindIII fragment of HSV-2 into the joint region of the HSV (see p.6). Thus, applicant has express possession of only one such modification, in a genus which comprises thousands of different possibilities. It is pointed out

that the claims is not specifically limit the disruption of *any* γ1.34.5 gene, only that the disruption results in an intact γ1.34.5 gene. Therefore, a modification that does not disrupt any γ1.34.5 gene (such as a conservative substitution) is encompassed by the claims as written.

The written description guidelines note regarding such genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, no structural limitations or requirements which provide guidance on the identification of modifications which meet the functional limitations is provided (the functional limitation being that one γ1.34.5 gene is intact).

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that:

> "In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly,

> naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."

In the instant case, the claims encompass any modification of any inverted repeat such that one γ1.34.5 gene remains intact. There is no indication which specific modifications (other than the one disclosed) result in "one γ1.34.5 gene intact".

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that:

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, only one such modification is described.

Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of every modification resulting in one intact γ1.34.5 gene other than the one expressly disclosed. Therefore, the claims fail to meet the written description requirement by encompassing modifications which are not described in the specification.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the phrase, "a modification of an inverted repeat region of said HSV genome such that one γ1.34.5 gene remains intact and said amount of HSV being effective to reduce tumor mass." This recitation renders the claim indefinite because it is unclear in the modification is in a γ1.34.5 gene or a different region of the inverted repeat. Furthermore, the term "intact" is unclear because it is not defined in the specification and it is unclear if a modification consisting of a conservative substitution would result in an "intact" γ1.34.5 gene. Furthermore, the specification only refers to the $_{\gamma 1}$34.5 gene, not the γ1.34.5 gene. This is believed to be a typographical error, and the γ1.34.5 gene is considered to be the $_{\gamma 1}$34.5 gene for examination purposes. However, amendment is required. Finally, the recitation "said amount of HSV being effective to reduce tumor mass" is unclear. A suggestion that would be clearer is "said amount of HSV being an amount effective to reduce tumor mass." Claims 2-9 are dependent claims and are rejected for the same reasons.

Claim Rejections - 35 USC § 102

Response to Arguments

The applicants arguments regarding the rejection of claims under 35 USC 102 are persuasive because (1) Martuzzi is drawn to a method of treatment wherein the two copies of

HSV $_{\gamma 1}$34.5 gene are disrupted; and (2) Advani (1997 and 1998) does not disclose that the rate of killing is faster than the rate of growth, which is required to result in the reduction of tumor mass.

Claim Rejections - 35 USC § 112, second paragraph

Claim 1 and its dependent claims were rejected under 35 USC 112 because the recitation "an individual" was unclear. Furthermore, claim 5 was rejected because the recitation "a unique region" was unclear.

Response to Arguments

Applicants' arguments regarding "an individual" are persuasive, and the rejection of claims based on the recitation "an individual" is withdrawn. However, Applicants arguments regarding the recitation "a unique region" have been considered but are not persuasive because although the terms "long unique region" and "short unique region" are well known descriptions of regions of the HSV genome, the recitation "a unique region" is still indefinite because "a unique region" could also refer to any sequence in the HSV genome that is unique, not just the long unique region or the short unique region. Therefore "a unique region" can be considered to be a region other than the long and short unique regions. Amending the claim to recite "the long unique region or the short unique region" would obviate this rejection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
October 9, 2002

JEFFREY FREDMAN
PRIMARY EXAMINER